REMARKS

Applicant hereby submits the Fourth Supplemental Declaration of Richard Heuser, M.D., F.A.C.C., F.A.C.P. (attached hereto as Exhibit A) and the Third Supplemental Declaration of Andrew E. Lorincz, M.D. (attached hereto as Exhibit B). Both of these declarations were filed in co-pending application Serial No. 09/794,456 and support the fact that the genetic material language in Applicant's specification describes using both genes and cells for growing arteries. Accordingly, one skilled in the pertinent art apprised of Applicant's specification would understand that it discloses administration of a growth factor, including cells, to the leg of a patient to grow an artery in the heart, leg, or other areas of the body. See Capon v. Eshhar v. Dudas, 76 USPQ 2d 1078, (Fed. Cir. 2005).

To the extent that the Examiner may question the operability of using a growth factor, i.e., cells, for growing an artery in the leg of a human patient, The Lancet article published August 10, 2002, entitled "Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomized controlled trial" (attached hereto as Exhibit C) reports a randomized controlled human trial establishing that autologous implantation of stem cells via injection into the leg resulted in artery growth. Artery growth was confirmed by independent autopsy findings.

Applicant also submits the May 2000 NIH publication entitled, "Stem Cells: A Primer" (attached hereto as Exhibit D) and an article entitled, "Stem Cells" that appeared in the August 7, 2006 issue of Time magazine (attached hereto as Exhibit E). Both publications clearly demonstrate that embryos, such as the two-cell embryo of Lutjen et al., are not stem cells. The two-cell embryo, after implantation, forms a hollow ball of cells called the blastocyst. Embryonic stem cells form on the inside of the blastocyst creating the inner cell mass. Clearly, it

is unreasonable and scientifically incorrect to make any assertion that the implantation of a two-cell embryo responds to the implantation of a stem cell.

The following evidence supports Applicant's statement that the invention uses old and well-known administration techniques and materials. Regarding pre-filing knowledge in the art of the disclosed and claimed administration techniques, the Examiner is referred to the Declaration of G. Robert Meger, M.D. (of record). Also see U.S. Patent No. 5,328,470 granted to Nabel, et al. (hereinafter referred to as "Nabel" and attached hereto as Exhibit F) that discloses administering a different class of cells to a human patient via angioplasty. See Capon v. Eshhar v. Dudas, supra.

Regarding the use of old materials, the claimed cells are notoriously old. See, for example, the Caplan 1991 publication (of record in the Sixth Supplemental Information Disclosure Statement).

Applicant points out that the specification describes both broad and specific methods of administering growth factors, including cells. The specification at page 45 clearly states that an artery can be grown "in the heart, legs, or other areas by injecting a gene or other genetic material (emphasis added) into muscle at a desired site." Examples 18, 33, 34, and 36 describe injection into the patient's leg to grow an artery, and Example 19 describes injection into a patient's cardiac muscle via "open heart surgery, endoscopic surgery, direct injection of the needle without incision, or by any other desired means." Those skilled in the art, having read Applicant's specification, would understand that Applicant's use of the term "genetic material" includes cellular growth factors broadly comprising cells and, specifically, stem cells and germinal cells. The Examiner is requested to consider such material fact and to properly construe Applicant's disclosed invention as being drawn to growth factor species including stem

cells and germinal cells. Indeed, it is incumbent upon the Examiner, if she doubts or challenges the veracity of statements in an application, to cite scientific proof that they are false. The Strauer et al. publication (of record) does not suffice as scientific proof simply because this publication does not involve the administration of cells by injection.

The Lancet publication entitled, "Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomized controlled clinical trial" by Wollert et al. (attached hereto as Exhibit G) demonstrates that high-pressure injection is not required to grow an artery when balloon catheter administration is utilized. The Nabel patent constitutes further evidence that high pressure is not required.

The publication entitled, "Osiris Reaches Safety Milestone in Stem Cell Clinical Trial for Cardiac Patients" by Osiris Therapeutics, Inc. (attached hereto as Exhibit H) announces the U.S. Food and Drug Administration's (FDA's) approval of a Phase I Clinical Trial for intravenous administration of stem cells. Of particular importance is Osiris' reported use of a "standard IV line" with the expectation that implanted stem cells will migrate to the injured area of a heart as a result of the "body's own signals." It appears that the Osiris clinical trials follow Dr. Elia's disclosed IV heart repair technique. With the FDA's approval of such trials and the other evidence of record, there can be little question of the enablement of intravenous administration.

The Examiner's attention is further directed to the above-mentioned The Lancet publication (Exhibit C) wherein arteries were grown in patients having chronic arterial conditions, thereby providing further evidence that timing of treatment is not an essential element.

The article published in 2005 in Circulation by Dohmann et al. entitled, "Transendocardial Autologous Bone Marrow Mononuclear Cell Injection in Ischemic Heart

Failure" (attached hereto as Exhibit I) provides autopsy proof that arteries are grown in the body of a human patient through administration of cells.

Regarding dosages, the following evidence and remarks are submitted.

Examples 18, 19, 33, 34, and 36 specifically describe dosages for intramuscular injection. It would be a routine matter to apply proper dosages, via such well-known techniques as intramuscular, intravenous, or intraluminal administration, for at least several reasons.

Firstly, "... it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. ...." MPEP Section 2164.01 (c).

Secondly, during the concurrent examination of the Weiss U.S. Patent No. 6,844,312 granted by the Examiner (attached hereto as Exhibit J), the Examiner never raised the issue of dosages, either in the rejection or in the analysis of the Wands factors. Like the instant application, the Weiss patent did not describe a dosage range but rather described dosages at column 6, lines 19-27 as:

> An "effective amount" is an amount of a therapeutic agent sufficient to achieve the intended purpose. The effective amount of a given therapeutic agent will vary with factors such as the nature of the agent, the route of administration, the size and species of the animal to receive the therapeutic agent, and the purpose of the administration. The effective amount in each individual case may be determined empirically by a skilled artisan according to established methods in the art.

Both the Weiss patent and the instant application disclose specific dosages in their specifications, and their respective claims do not contain dosage limitations. It would not appear that the level of skill required to practice the invention of Weiss would be less than that of the present invention.

Thirdly, Applicant's specification describes artery growth and heart repair by direct injection of growth factor cells in dosage ranging from approximately 6.25 x 10^6 (Example 18) to approximately 12.5 x 10^6 (Example 19). Available off-the-shelf cDNA clones (nucleic acids) are directly injected into either the patient's cardiac muscle (Example 19) or the patient's leg (Example 18). Each example describes forming an artery with increased blood flow. Each example also discloses slowly injecting the growth factor to avoid any carry away. While these examples employ nucleic acids, one skilled in the art reading the specification, which teaches that cells, i.e., stem cells (BMC's) possess equivalent activity to genes (nucleic acids) and other genetic material in forming a new artery (i.e., promote morphogenesis of an organ—artery), would be able to easily extrapolate the number on a weight basis of mononuclear cells required to obtain equivalent results. Note in this regard that the 2002 publication of Strauer et al. (of record in the Third Supplemental Information Disclosure Statement) discloses injecting six (6) to seven (7) times with 1.5 to 4 x 10^6 cells without disclosing any difference in results over the entire dosage range. Therefore, there is no significant clinical difference between Applicant's 6.25 to 12.5 x 10^6 and Strauer et al.'s 9 to 28 x 10^6 dosage ranges. Further, such skilled person would understand that intravenous or intraluminal administration routes would generally require larger doses than the direct injection route of Examples 18 and 19 and, for example, simply doubling the dosage to 12.5 to 25 x 10^6 cells would essentially encompass Strauer et al.'s entire range. It is clear from Strauer et al. that there is no risk for over-dosing, particularly using autologous BMC's, which are contemplated in Applicant's specification.[1] cf. In re Bundy, 642 F. 2d 430, 434, 209 USPQ 48, 51-52 (CCPA 1981).

[1] The conversion for dosages of nucleic acids to corresponding dosages of cells was conducted as follows. Examples 18 and 17 specified dosages of 500 micrograms (ug) and 250 ug, respectively. The weight of nucleic acids of an average cell was considered to equal 40 picograms (pg). The described dosages of 250 and 500 ug when converted to pg by multiplying by 10^6 equals 250 x 10^6 pg and 500 x 10^6 pg. Since nucleic acids of an average cell have an average weight of

Fourthly, both Drs. Heuser and Lorincz have stated, in paragraph 8 of their respective Supplemental Declarations filed in co-pending application Serial No. 09/794,456, (attached hereto as Exhibits K and L, respectively) that dosages are a matter of routine medical practice and have then enumerated various factors that skilled physicians routinely consider in this regard. Such declarations raise a genuine issue of material fact that cannot be ignored by the Examiner.

The evidence proffered by Applicant in the above four paragraphs makes it clear that undue experimentation is not required to select an appropriate dosage in the practice of the claimed invention.

The Examiner is requested to fully consider the above evidence and accompanying remarks when formulating the next Office Action. Applicant believes that consideration of all evidence submitted in the instant application supports the allowance of claims 382-402 and an indication to such effect is respectfully requested. Should the Examiner have any questions or require additional information or discussion to place the application in condition for allowance, a phone call to the undersigned attorney would be appreciated.

Respectfully submitted,

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40 pg, a conversion is made by dividing 250 x 10^6 and 500 x 10^6 by 40 to arrive at the equivalent cell dosages, which are 6.25 x 10^6 and 12.5 x10^6, respectively.